PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/000155	22.01.2004	24.01.2003

International Patent Classification (IPC) or both national classification and IPC
C07K14/52, A61K38/19, A61P31/18

Applicant
PRIMM S.R.L.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Groenendijk, M Telephone No. +31 70 340-3715

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	3
	No:	Claims	1,2,4-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V.

The following document is referred to in this communication:

D1 : WO 00/27880 A (LUSSO PAOLO ; PRIMM SRL (IT); PAVONE VINCENZO (IT); SAN RAFFAELE CENTR) 18 May 2000 (2000-05-18)

I.NOVELTY

Document D1, which is considered to represent the most relevant state of the art, discloses fragments of RANTES based on the domain (10-34) and their use in the treatment of HIV-infection. One embodiment is Ac-CFAYIARPLPRAHIKEYFY-NH2 (Ac-RANTES(11-29)-NH2).

From this, the subject-matter of independent claim 1 differs in that in position 3 a proline residue is substituted for the alanine residue and that the N-terminal part Ac-CXPYI is connected to the C-terminal XY-NH2 part via a spacer peptide having 2-12 amino acid residues.

It is true that in D1 a proline residue in position 3 was mentioned as part of a list of substituents. However only in the framework of a Markush formula having many lists of substituents.

Hence the claims 1-7 are considered to be novel under art.33(2) PCT.

II.INVENTIVE STEP

1)The closest prior art is considered to be D1 as discussed in Section I.

2)The effect of the difference of the present compounds with the closest prior art compound, actually only the proline residue in position 3, is a higher activity.

3)The problem to be solved by the present invention may therefore be regarded to be the provision of RANTES based peptide analogs having a higher activity.

4)No suggestion or indication was made in the prior art as to the introduction of a proline residue in position 3, resulting in an improved activity. Therefore said introduction cannot be considered to be an obvious modification.

Hence the compounds of the invention that actually solve the problem posed, that is exhibit unexpected advantageous properties, particularly an improved activity, are considered to involve an inventive step.

However claim 1 encompasses compounds having a completely undefined spacer peptide which actually can embody the major part of the compounds in the form of (Ala)12 or can even be as short as only two amino acid residues. It is therefore

considered to be very unlikely that all compounds claimed in claim 1 actually solve the problem posed. Said objection also applies, mutatis mutandis, to the claim 2 and the claims 4-7 as far as relating to said compounds.
Hence the claims 1,2 and 4-7 are considered to lack an inventive step under Art.33(3) PCT.